Sigmoid colon metastasis after radical nephrectomy for clear cell renal carcinoma: a case report and literature review

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**Sigmoid colon metastasis after radical nephrectomy for clear cell renal carcinoma:**

**a case report and literature review**

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1 Abstract

Background: Metastasis of renal cell carcinoma most commonly occurs in the lungs, lymph nodes, bones, liver, and brain. It is rare for CCRCC to metastasize to the sigmoid colon after radical nephrectomy, which often signifies systemic metastasis and poor prognosis.

Case Presentation: A 65-year-old woman was hospitalized for bloody stools, and she had a radical nephrectomy eight years ago after being diagnosed with CCRCC. The preoperative colonoscopic biopsy failed to clarify the nature of the mass, and the imaging examination suggested that the mass may be malignant. Following surgery to remove the mass, it was diagnosed as sigmoid metastatic CCRCC according to histopathology and immunohistochemistry. At present, she was in good health, and no clinical or radiological evidence of metastasis was found in her 11-month follow-up after surgery.

Conclusion: Metastasis may take a long time to appear after radical nephrectomy, so it is essential to actively follow up and review patients who have undergone renal cancer surgery, and early detection and treatment of metastases remain crucial.

2 Background

Renal cell carcinoma (RCC) is one of the common malignant tumors in the world, accounting for about 3% to 5% of all malignant tumors [1]. The most common type of RCC is clear cell renal carcinoma (CCRCC), which
accounts for 70% of all cases [2]. About one-third of patients have already developed metastasis when diagnosed with the disease. Most commonly, metastatic sites of RCC include the lungs, lymph nodes, bone, brain, and liver [3].

Metastasis of the digestive tract is relatively rare, especially colorectal. Data on 32 cases are available in the global literature database. Herein, we report a case of sigmoid colon metastasis 16 years after radical nephrectomy for CCRCC and summarize previous case reports of similar diseases. This case report is of value in understanding the metastatic pattern of renal cell carcinoma.

3 Case demonstration

A 65-year-old woman was admitted to the hospital with blood in her stool for more than one month in 2020. She was diagnosed with clear cell carcinoma of the right kidney in 2012 and underwent radical resection. Unfortunately, she was back in the hospital six years later due to a mass of 3cm*3cm in the right adrenal gland area on a CT scan of the abdomen. She underwent right adrenalectomy, and pathology revealed metastatic carcinoma of CCRCC from the right kidney. After the second year of adrenalectomy, the patient developed blood in the stool, and during the colonoscopy, a sigmoid mass was observed, which biopsy pathology showed inflammation necrosis tissue. Her abdominal CT revealed that the sigmoid colon mass had noticeable enhancement. The patient's history of recurrence of renal cancer prompted us to perform PET-CT imaging on the patient. The results showed an abnormally increased glucose metabolism in the lower sigmoid colon, pointing toward the possibility of malignancy. The patient underwent sigmoid colectomy, and postoperative pathology showed that the tumor measured 4.3*3*2.5cm, infiltrating to the total thickness. There was no evidence of metastasis in all 12 peri-intestinal lymph nodes, and the surgical margins were negative. The patient was eventually diagnosed with clear renal cell sigmoid colon metastasis and was discharged on the sixth day after the operation. At present, she was in good health, and no clinical or radiological evidence of metastasis was found in her one-year follow-up after surgery.

4 Discussion

As one of the most common malignancies of the urinary system, RCC composes 3%~5% of all malignant tumors [4]. It is characterized by high mortality rates and recurrence rates. About a third of RCC patients
will develop metastatic disease, and these metastatic sites can occur anywhere in the body. The most common metastatic sites are the lung, bone, lymph nodes, liver, and brain. About 40% of advanced patients have two or more organ metastases [5].

A total of 32 cases of colorectal metastasis associated with RCC were identified in the Pubmed database, including 24 males (75%), 5 females (15.6%), and 3 cases that were not reported. The median time from nephrectomy to the discovery of metastatic disease is 5 years, and the average is 6.2 years. According to the location of metastasis, there were 1 case (3.1%) in the cecum, 4 cases (12.5%) in ascending colon, 6 cases (18.8%) in hepatic flexure of the colon, 4 cases (12.5%) in the transverse colon, 2 cases (6.3%) in splenic flexure of the colon, 3 cases (9.4%) in descending colon and 8 cases in the sigmoid colon, of which solitary metastasis accounted for 40.6%. A total of 24 patients chose surgical resection, and only four chose conservative treatment, which the therapy plans of other patients are not mentioned in the literature.

4.1 Auxiliary examination

4.1.1 Abdominal CT

The abdominal CT is a routine preoperative imaging examination for patients with colorectal cancer. In addition to determining the location of the primary tumor, it can also be used to determine whether there are metastases in the liver, lymph nodes, and other intra-abdominal organs. CT images of the case showed the soft tissue density of the sigmoid colon in the pelvis. The area of focus was significantly enhanced, indicating the intestinal metastasis has a very abundant blood supply, which differs from the imaging findings of colorectal carcinoma. The most common sigmoid colon adenocarcinomas are ulcerative masses, which appear as circular enhancements along the affected bowel wall under CT imaging. However, according to the previous studies, primary colorectal adenocarcinoma adenocarcinomas are rarely enhanced to such an extent by contrast agents [6]. The degree of tumor enhancement under CT images is mainly determined by the density of internal blood vessels. As for primary RCC lesions, different subtypes have varying levels of enhancement. CCRCC has the highest enhancement degree, while metastatic lesions show similar phenomena [7], and the enhancement of non-CCRCC metastatic lesions is generally lighter [8]. In our case, the CT value of the enhanced mass was significantly greater than that of common intestinal adenocarcinoma, and the metastasis appeared as a round mass protruding into the intestinal cavity, with relatively clear borders, similar performance was described in previous case reports [9].
4.1.2 PET-CT

PET-CT can be used to evaluate the metastasis of tumors and the benign and malignant tumors. PET-CT has an 86% sensitivity and an 88% specificity for diagnosing renal cancer metastases [10]. The ability of PET-CT to distinguish RCC colorectal metastases has been demonstrated in a previous case report [11]. Presently, PET-CT has been widely used in the diagnosis of CCRCC. In this report, the patient did not receive positive results from the colonoscopy. PET-CT was performed after reviewing the patient's history of recurrence of renal cancer and the abdominal CT with the results indicating malignancy.

4.1.3 Colonoscopy

Colonoscopies are clinically necessary for all patients with gastrointestinal bleeding, regardless of the cause. Compared with radiographic examinations like abdominal CTs and MRIs, colonoscopy provides superior specificity and sensitivity for diagnosis. For CCRCC sigmoid colon metastasis cases that are extremely rare, colonoscopy plus pathological biopsy may be the best alternative. Still, the pathology of the patient's colonoscopy biopsies failed to explain the nature of the mass. This phenomenon may be related to superficial tissue sampling, necrosis of the tumor, and inflammation and exudation of the surrounding tissues.

4.1.4 Pathology and immunohistochemistry

Colonic metastases of RCC and colorectal primary adenocarcinoma are both seen as masses that protrude into the intestinal cavity under colonoscopy, and histopathology and immunohistochemistry of gross tissue are the key determinants of disease diagnosis. For CCRCC, tumor cells are generally round or polygonal with clear contours filled with glycogen and lipids under the microscope, which appear transparent. In addition, there are numerous capillaries and sinuses in the mesenchyma [12]. An indispensable part of the diagnosis of kidney tumors is the immunohistochemical markers. As members of the paired box gene family, PAX2 and PAX8 play a crucial role in developing tissues and organs during the embryonic stage of an animal's life. As the body matures, they slowly decline and vanish in normal tissues and cells. In mature kidney tissues, high levels of PAX2 and PAX8 indicate the presence of tumors. For CCRCC, the positive PAX2 ratio ranges from 84% to 95% [13]. PAX2 has a sensitivity of 77%~85% and a specificity of 90%~97% in CCRCC metastases [14, 15]. Similar to PAX2, PAX8 is highly expressed in CCRCC cells (about 95% of primary foci and about 93% of metastatic foci), and PAX8 is more sensitive than PAX2 in diagnosing renal malignancies [13]. Physicians typically combine PAX2 and PAX8 for the diagnosis of metastatic CCRCC. The carbonic anhydrase 9 (CA-IX)
is a transmembrane protein that regulates the intracellular pH value and is rarely found in normal kidney tissues. Statistics indicate that CA-IX is expressed by 94%~97% of CCRCC cells, while its presence in chromophobe cell carcinomas and papillary renal carcinomas is relatively low [16]. The level of CA-IX expression can also be related to the prognosis of patients, as higher expression indicates a lower stage and grade of the tumor [17].

Another good marker for distinguishing CCRCC from other subtypes of RCC is Vimentin. Several studies have revealed that vimentin was present in the cytoplasm of CCRCC, with a positive rate of 54.5%~100%. At the same time, its presence in other subtypes was rare, and only 0%~20% (Chromophobe cell carcinoma) and 0%~9.7% (eosinophilic cell carcinoma), respectively [18-23]. Additionally, in mRCC, high vimentin expressions are associated with poorer overall survival [24]. Different types of RCC express different amounts and types of cytokeratin in their tissues. For example, CK18 is expressed in all renal malignancies, while CK20 is all negative. CK7 usually appears in papillary RCC and chromophobe cell carcinoma but rarely in CCRCC (0~7%) [19, 20]. The sensitivity of CD10 for the diagnosis of mRCC is 83%~100% [25, 26]. As CD10 is also widely expressed in many common malignancies, its specificity is low, so it is currently used mainly for the differential diagnosis of adrenal cortical tumors and RCC adrenal metastases [25]. RCC antigen is a normal brush edge antigen of the human proximal tubule and is expressed prominently in papillary RCC (95%), CCRCC (72%), and chromophobe cell carcinoma (91%), but only 40% in mRCC [27]. Similar to CD10, RCC antigen is expressed frequently in breast, colon, prostate, adrenal, and other cancers (17%~100%), so the specificity is poor and cannot be used alone to diagnose RCC [27]. Overexpression of TFE3 is mainly used for the diagnosis of the Xp11.2 translocation RCC [28]. A strong expression of S-100 is observed in 70%~96% of urothelial carcinoma but is almost rarely observed in RCC, which can be used to distinguish between the two types of carcinoma [29].

Until now, no specific marker has been found for the CCRCC, and its diagnosis mainly depends on combining the markers mentioned above to differentiate it from other types of RCC. In this case, the tumor cells of sigmoid colon metastasis were positive for vimentin, Pax8, CA-IX, Ki-67, and CD10 but negative for CK20, CK7, RCC markers, TFE3, and S-100.

4.2 Metastatic Pathways

There are three metastasis pathways of RCC: hematogenous spreading, lymphatic spreading, and direct invasion. It does not appear that there is any close connection between the blood supply and lymphatic
drainage of the kidney and colon, except for the return of blood through the inferior vena cava. Direct tumor invasion or incorrect surgical intervention may result in new cancerous cells being planted and spreading in the abdominal cavity, but in this case, we excluded this possibility. First of all, according to the gross specimen, the colon metastasis grows from the intestinal wall, instead of infiltrating from the serosal side from the outside to the inside. Secondly, the previous two operations of the patient were performed by using the retroperitoneal approach to remove the kidney and adrenal glands. Therefore, the abdominal cavity was not open, and there was no possibility of tumor implantation. As metastatic lymph nodes of mRCC primarily are located in the retroperitoneal region and the hilus of the kidney region, no swelling of lymph nodes was observed in this area, indicating that lymphatic metastasis was not the cause of colonic metastasis. In the end, circulating tumor cells (CTC) and venous thrombosis may explain the phenomena. The presence of CTC is related to the stage and prognosis of mRCC. There was evidence that 46.7% of patients with mRCC can detect CTC in their peripheral blood; the number of CTCs affects the patient's overall survival (OS), progression-free survival (PFS), and disease-free survival (DFS) [30], and 62% of patients with positive CTC develop metastatic disease within two years [31]. As the intestines have a rich blood supply, the chance for metastasis is much greater than for other organs with a weak blood supply. Thrombosis of the renal vein and inferior vena cava also is the leading cause of cancer cells entering the blood. According to statistics, approximately 27% of patients with mRCC have thrombosis, and the longest thrombus can extend from the renal vein to the right atrium [32]. On the one hand, a more giant thrombus can facilitate the entry of tumor cells into the peripheral circulation. On the other hand, thrombosis may cause blood reflux, which can cause tumor cells to spread to some organs, such as the adrenal gland, the ovary, the testis, and the colon. Interestingly, the patient in our case also had a history of RCC adrenal metastases.

4.3 Treatment and prognosis

According to location, metastases can be divided into typical metastasis such as liver, lung, bone, lung, adrenal glands, and atypical metastasis such as breast, small intestine, colorectal, stomach, pancreas, etc. Clinical symptoms are rarely present in patients with typical metastasis. In contrast, patients with atypical metastasis generally experience symptoms related to metastatic organs, such as blood in the stool and abdominal pain. Among the patients with RCC colorectal metastases counted in this article, 46.7% had symptoms of lower gastrointestinal bleeding, 33.3% had abdominal pain, and only 13.3% had no clinical symptoms. However, there does not seem to be a direct relationship between the location of the metastasis and
the prognosis. Researchers found that the outcome of patients with atypical metastasis undergoing surgical resection is the same as that for patients with lung metastasis [33]. Different from common malignant tumors like stomach cancer, some patients with mRCC can still benefit from palliative surgery to remove the metastases, which can significantly improve their prognosis, especially for overall survival (OS) and cancer-specific survival (CSS) [34-36]. Surgery is not always a viable option for patients with mRCC. For example, T4 stage mRCC patients who were in the status of N1 stage or older than 76 years, there is no difference in overall survival between cytoreductive nephrectomy and non-surgical treatment [37]. Additionally, some mRCC patients may show slow development of metastatic tumors. Developing a risk classification and monitoring plan for each patient with mRCC instead of starting systemic treatment from the beginning will not affect the later treatment effect and avoid some toxic side effects caused by systemic therapy [38].

5 Conclusion

During clinical practice, it is rare for patients to develop colorectal metastatic disease after radical nephrectomy. In this report, we describe the case of sigmoid colon metastasis after surgery for CCRCC. After being diagnosed with CCRCC, the patient underwent three surgeries (primary tumor on the right kidney, metastatic tumor right adrenal gland, and sigmoid colon), and now she still live a good life. It is crucial for patients who have undergone renal cancer surgery to follow up and review actively, and detect and treat metastases early. Moreover, it is essential to integrate multiple examinations in the follow-up of mRCC after surgery, especially for patients whose colonoscopy indicates polyps, adenomas, or masses and the pathology is negative, a further abdominal CT or PET-CT examination is needed. With the help of radiology and the patient's medical history, symptoms, and physical examination, a sufficient differential diagnosis can be drawn to determine the most appropriate course of treatment.

6 Table

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<th>Cases published in the literature on metastatic RCC to the colon and rectum</th>
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M, male; F, female; N/A, not available; RCC, renal cell carcinoma; CCRCC, clear cell renal cell carcinoma.
The preoperative evaluation and intraoperative condition of the patient. (A-1) The abdominal CT scan revealed a nodule that measured about 1 cm in diameter in the sigmoid colon of the patient more than one year ago. (A-2) In the same abdominal CT examination one year later, the image shows a soft tissue mass in the sigmoid colon, which is much larger than before, with a diameter of about 3 cm, and there is an apparent arterial phase enhancement. (A-3) There was a 3 cm diameter round adrenal mass found in the patient with 6 years after the first surgery, and following surgical removal of the mass, pathology revealed metastases of CCRCC. (B-1-2) Endoscopic image of the mass lesions in the sigmoid colon. About 22 cm from the anus, an approximately 3- to 4-cm sigmoid mass was visible, with necrotic tissue covering the surface. (C) The mass was completely removed by laparoscopic surgery and found in the lower part of the sigmoid colon, with a diameter of about 4 cm.

The FDG-PET/CT images of sigmoid colon tumor: (A1-3) FDG PET/CT images of the pelvic cavity in Axial view. (B1-2) FDG PET/CT images of the pelvic cavity in sagittal view. (C1-2) FDG PET/CT images of the pelvic cavity in coronal view.
Figure 3

Histopathological and immunohistochemical examination of sigmoid colon specimen: 

(A): A low-magnification image shows a metastatic CCRCC in the colon.---hematoxylin-eosin, original magnification 40×. 

(B): Clear cells with round or polygonal shapes are arranged in sheets, with clear outlines, transparent cytoplasm, and a few surrounding fibrovascular interstitials.---hematoxylin-eosin, original magnification 100×. 

(C) vimentin, (D) CA-IX, (E)CD10, (F) CDX-2.

Ethics approval and consent to participate

This study was approved by the ethics committee of Shaoxing people's Hospital and obtained the written informed consent of the subjects.

Consent for publication

Written informed consent was obtained from the subject.

Competing interests

The authors have no conflicts of interest to disclose.

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Authors’ contributions

Hao Che examined the data, did the analysis, wrote the manuscript. Yuechao Yao, Zian Wang, Zhiliang Chen, GuoJiang Tian did the
surgical intervention and conducted the post-operation follow-up. The radiologic images provided by Zengxin Lu and the pathological data provided by Xibo Liu. Zhenjun Li and Xiaojiang Ying conduct the final supervision and editing of the manuscript and obtain the fund support. All authors read and approved the final manuscript.

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8 Reference


